PREVALENCE OF VITAMIN B_{12} DEFICIENCY IN ELDERLY

Dissertation submitted in

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CERTIFICATE

This is to certify that the dissertation entitled "**PREVALENCE OF VITAMIN B_{12} DEFICIENCY IN ELDERLY**" is a bonafide work done by **Dr.BIJIN OLIVER JOHN.**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in Geriatric Medicine (Branch-XVI) under my guidance and supervision during the academic year 2009 -2012.

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DECLARATION

I solemnly declare that this dissertation entitled "**PREVALENCE OF VITAMIN B_{12} DEFICIENCY IN ELDERLY**" was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2009-2012 under the guidance and supervision of **Prof.Dr.B.KRISHNASWAMY M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in Geriatric Medicine (Branch-XVI).

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Date:

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CONTENTS

INTRODUCTION

Low serum Vitamin B_{12} levels become more common with aging. It has been recently found that approximately 10% to 15% of older adults have Vitamin B_{12} deficiency. The older the patient and the more profound the signs and symptoms, the less likely the recovery.

Vitamin B_{12} deficiency can present clinically as a hematologic disorder that causes macrocytosis and anemia or a neurological disorder that can cause a peripheral neuropathy and spinal cord lesions or with neuropsychiatric manifestations, including delirium, depression, confusion, memory loss and poor language, comprehension and expression. Since patients with more severe hematologic signs often have less neurologic impairment and vice versa, it is important to consider vitamin B_{12} deficiency even if the patient lacks macrocytosis and anemia.

Thus, although serum Vitamin B_{12} levels become low with aging it often goes unnoticed. Hence screening of all older adults for vitamin B_{12} should be considered and supplementation of all deficient patients is recommended.

REVIEW OF LITERATURE

Vitamin B_{12}, also called **cobalamin**, is a water-soluble vitamin with a key role in the normal functioning of the brain and nervous system, and for the formation of blood. It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid synthesis and energy production. It is the largest and most structurally complicated vitamin and can be produced industrially only through bacterial fermentation-synthesis.

Cobalamin (vitamin B_{12}) exists in a number of different chemical forms. All have a cobalt atom at the center of a corrin ring. In nature, the vitamin is mainly in the 2-deoxyadenosyl form, which is located in mitochondria. It is the cofactor for the enzyme methylmalonyl CoA mutase. The other major natural cobalamin is methylcobalamin, the form in human plasma and in cell cytoplasm. It is the cofactor for methionine synthase.

Dietary Sources and Requirements

Cobalamin is synthesized solely by microorganisms. Ruminants obtain cobalamin from the foregut, but the only source for humans is food

of animal origin, e.g., meat, fish, and dairy products. Vegetables, fruits, and other foods of non-animal origin are free from cobalamin unless they are contaminated by bacteria. **Herrmann. W** and **Geisel. J** in 2002 studied the influence of vegetarian lifestyle on vitamin B_{12} status in the body(1). Adult daily losses (mainly in the urine and feces) are between 1 and 3 g (~0.1% of body stores) and, as the body does not have the ability to degrade cobalamin, daily requirements are also about 1–3 g. Body stores are of the order of 2–3 mg.

Rajan S and **Wallace JI et al** in 2002 described the prevalence of cobalamin (Cbl) deficiency in older adult outpatients and to determine whether regular intake of a synthetic source of cobalamin confers protection against Cbl deficiency(2).

Absorption

Two mechanisms exist for cobalamin absorption. One is passive, occurring equally through buccal, duodenal, and ileal mucosa; it is rapid but extremely inefficient, <1% of an oral dose being absorbed by this process. The normal physiologic mechanism is active; it occurs through the ileum and is efficient for small (a few micrograms) oral doses of cobalamin and is mediated by gastric intrinsic factor (IF). Dietary cobalamin is released from protein complexes by enzymes in the

stomach, duodenum, and jejunum; it combines rapidly with a salivary glycoprotein that belongs to the family of cobalamin-binding proteins known as haptocorrins (HCs). In the intestine, the haptocorrin is digested by pancreatic trypsin and the cobalamin transferred to IF. IF is produced in the gastric parietal cells of the fundus and body of the stomach. The IF-cobalamin complex passes to the ileum, where IF attaches to a specific receptor (cubilin) on the microvillus membrane of the enterocytes. The cobalamin-IF complex enters the ileal cell where IF is destroyed. After a delay of about 6 hours, the cobalamin appears in portal blood attached to transcobalamin (TC) II. Between 0.5 and 5.0 g of cobalamin enters the bile each day. This binds to IF, and a major portion of biliary cobalamin is normally reabsorbed together with cobalamin derived from sloughed intestinal cells. Because of the appreciable amount of cobalamin undergoing enterohepatic circulation, cobalamin deficiency develops more rapidly in individuals who malabsorb cobalamin than it does in vegans, in whom reabsorption of biliary cobalamin is intact**. Swain R** in **1995** reviewed information on cyanocobalamin (Vitamin B_{12}) deficiency, changing options in laboratory testing for deficiency states, and options for treatment(9). High-risk groups for the deficiency syndrome included the elderly, patients taking ulcer medications over long periods, patients

with AIDS, vegetarians, patients who had undergone stomach resection or small bowel resection, and patients with dementia.

Transport

Two main cobalamin transport proteins exist in human plasma; they both bind cobalamin—one molecule for one molecule. One Haptocorrin, known as Transcobalamin I, is closely related to other cobalamin-binding HCs in milk, gastric juice, bile, saliva, and other fluids. These HCs differ from each other only in the carbohydrate moiety of the molecule. TC I is derived primarily from the specific granules in neutrophils. Normally, it is about two-thirds saturated with cobalamin, which binds it tightly. TC I does not enhance cobalamin entry into tissues. Glycoprotein receptors on liver cells are involved in the removal of TC I from plasma, and TC I may have a role in the transport of cobalamin analogues to the liver for excretion in bile. The other major cobalamin transport protein in plasma is TC II. This is synthesized by liver and by other tissues, including macrophages, ileum, and endothelium. It normally carries only 20–60 ng of cobalamin per liter of plasma and readily gives up cobalamin to marrow, placenta, and other tissues, which it enters by receptor-mediated endocytosis.

Vitamin B_{12} belongs to the family of cobalamins and serves as a cofactor for two important reactions in humans. As methylcobalamin, it is a cofactor for methionine synthetase in the conversion of homocysteine to methionine, and as adenosylcobalamin for the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA.

Aetiology(4)

The causes of vitamin B_{12}deficiency in elderly are as follows;

- Atrophic gastritis and hypochlorhydria (**Andrews GR et al 1967**)(5)
- Chronic antacid use (H-2 blockers, PPIs) { **Howden CW-2000**}(6)
- Gastric surgery (**Sumner AE et al 1996**)(7)
- Ileal surgery
- Diseases of the small intestine and terminal ileum: Crohn's disease, sprue, malabsorption syndromes
- Helicobacter pylori infection
- Pancreatic insufficiency

- Parasitic infections of small bowel (eg; fish tapeworm)
- Bacterial overgrowth syndromes
- Strict vegetarianism
- Acquired Immunodeficiency Syndrome (AIDS) and AIDS treatment (e.g: zidovudine)
- Pernicious anemia
- Possibly metformin

Pathogenesis of Cobalamin Deficiency

Nutritional Cobalamin Deficiency

Vegetarianism is an important cause of nutritional cobalamin deficiency in developing countries.

Inadequate Dissociation of Cobalamin from Food Protein

Dietary cobalamin requires proteolytic digestion of food by gastric acid and pepsin and failure to release cobalamin from food protein can lead to cobalamin deficiency despite the presence of intrinsic factor.

Absent Secretion

Deficiency of intrinsic factor as a result of gastric parietal cell atrophy is associated with insufficient HCl secretion and can be caused by (1) total or partial gastrectomy, (2) autoimmune destruction (chronic atrophic gastritis) as found as in classic pernicious anemia, or (3) destruction of gastric mucosa by caustic (lye) ingestion.

Total gastrectomy invariably leads to cobalamin deficiency in 2 to 10 years, thus warranting prophylactic cobalamin (and iron) replacement. After partial gastrectomy, up to a third of patients may have multifactorial cobalamin deficiency from decreased secretion of intrinsic factor, hypochlorhydria, or intestinal bacterial overgrowth of cobalamin-consuming organisms. Morbidly obese patients who have undergone gastric bypass surgery have more malabsorption of cobalamin from food than do those treated by vertical banded gastroplasty. Malabsorption of cobalamin can also occur with the long-term use of H2 blockers or proton pump inhibitors.

In pernicious anemia, the primary event is autoimmune destruction and atrophy of the gastric parietal cell mucosa, thereby leading to the absence of intrinsic factor and HCl, which causes severe cobalamin malabsorption and deficiency. The autoimmune gastritis that eventually

leads to chronic atrophic gastritis involves the gastric fundus and body. Intrinsic factor antibodies are found in the serum of 60% and in the gastric juice of 75% of patients with pernicious anemia. Type I anti–intrinsic factor antibodies prevent binding of cobalamin to intrinsic factor, whereas type II anti–intrinsic factor antibodies prevent binding of intrinsic factor–cobalamin complexes to ileal intrinsic factor–cobalamin receptors and can interfere with tests for cobalamin absorption.

Abnormal Events Precluding Absorption of Cobalamin

Pancreatic insufficiency with a deficiency of pancreatic protease will fail to break down the R proteins to which cobalamin is preferentially bound in the stomach, thereby precluding transfer of cobalamin to intrinsic factor. However, with the widespread early use of pancreatic replacement, frank cobalamin deficiency is now uncommon. Endogenous pancreatic protease can be inactivated by massive gastric hypersecretion arising from a gastrinoma in Zollinger-Ellison syndrome, where the low pH of the luminal contents in the ileum can also preclude binding of the intrinsic factor–cobalamin complex with intrinsic factor–cobalamin receptors, a process that requires a pH higher than 5.4.

Bacterial overgrowth in the small bowel (arising from stasis, impaired motility, and hypogammaglobulinemia) favors colonization by

bacteria, which can then usurp free cobalamin before it can bind to intrinsic factor; this problem can be reversed by a short course of antibiotic therapy. Individuals heavily infested with the fish tapeworm Diphyllobothrium latum can become cobalamin deficient when these 10-m-long adult worms in the jejunum avidly usurp cobalamin. After the worms have been expelled (praziquantel, 10 to 20 mg/kg, single dose orally), cobalamin replenishment is curative.

Disorders of the Intrinsic Factor Receptors or Mucosa

Because the distal ileum has the greatest density of intrinsic factor–cobalamin receptors, removal, bypass, or dysfunction of only 1 to 2 ft of terminal ileum can result in cobalamin malabsorption. Among drugs, biguanides (i.e., metformin) decrease intrinsic factor and acid secretion and can inhibit transenterocytic transport of cobalamin in up to a third of patients, which can be avoided by intake of calcium (1.2 g/day). Other drugs (extended-release potassium chloride, cholestyramine, colchicine, and neomycin) can also impair transepithelial transport of cobalamin and interfere with the Schilling test.

Acquired Cobalamin Deficiency

Nitrous oxide (N2O) irreversibly inactivates cobalamin and results in a state of functional intracellular cobalamin deficiency, which can be bypassed by administration of 5-formyl-THF (leucovorin). Although N2O exposure during prolonged surgery can induce megaloblastosis, especially in those with marginal or low cobalamin stores, chronic intermittent (surreptitious, accidental, or occupational) exposure leads more frequently to a neuromyelopathic manifestation.

Clinical presentations of vitamin B_{12} deficiency

Physical examination of cobalamin-deficient vegetarians or those with pernicious anemia may reveal well-nourished individuals. By contrast, patients with folate deficiency are poorly nourished and may have other stigmata of multiple deficiencies from malabsorption. Varying degrees of pallor with lemon-tint icterus are common features of megaloblastosis. The skin may reveal either a diffuse brownish pigmentation or abnormal blotchy tanning. Premature graying is observed in both light- and dark-haired individuals.

Examination of the mouth may reveal glossitis with a smooth (depapillated), beefy red tongue and occasional ulceration of the lateral

surface. Thyromegaly may be observed in the neck if there is associated autoimmune disease. The characteristic findings of cardiovascular failure from severe anemia may be accompanied by mild splenomegaly and extramedullary hematopoiesis.

Nutritional cobalamin deficiency in developing countries can be manifested as florid pancytopenia, mild hepatosplenomegaly, fever, and thrombocytopenia, with the neuropsychiatric syndrome developing as a later manifestation. However, cobalamin-related neurologic disease has also been found in patients with only mild to moderate anemia secondary to cobalamin deficiency in both developing and developed countries. Between 25 and 50% of patients who have neuropsychiatric abnormalities attributable to cobalamin deficiency can have a normal hematocrit and MCV if they have adequate folate stores to protect them from hematologic abnormalities**. Dharmarajan TS et al** in **2003** did a study to identify subtle symptoms in older adults due to vitamin B_{12} deficiency and recognized that food - cobalamin malabsorption is the most common cause of the deficiency.(8)

Vitamin B_{12} Deficiency and Anemia

Megaloblastosis

To establish the diagnosis of megaloblastosis, the evaluation begins with a complete blood count, MCV (which often reveals a steady increase over a period of several months or years), peripheral smear, and reticulocyte count . Classic megaloblastosis from cobalamin deficiency may be accompanied by a hemoglobin level of less than 5 g/dL. Neutropenia and thrombocytopenia occur less commonly than anemia and are not usually severe. Occasionally, however, neutrophil counts less than 1000/μL and platelet counts less than 50,000/μL can be seen. Additional abnormalities supporting intramedullary hemolysis include elevated levels of serum lactate dehydrogenase and bilirubin, as well as decreased serum haptoglobin levels.

Megaloblastic anemia can be masked when there is a coexisting condition that neutralizes the tendency to generate large cells, such as with iron deficiency or thalassemia and it can be identified by giant myelocytes and metamyelocytes in bone marrow and hypersegmented neutrophils in bone marrow and peripheral blood. This problem is clinically relevant because appropriate replacement with cobalamin will elicit a maximal hematologic response only when any associated iron

deficiency is corrected. Conversely, if combined iron and cobalamin deficiency (after gastrectomy) is treated with iron alone, megaloblastosis will be unmasked. Thus, the diagnosis of megaloblastic anemia should not be excluded until bone marrow aspirates have been examined and the presence of bone marrow iron is established.

Peripheral blood – oval macrocytes, usually with considerable anisocytosis and poikilocytosis are the main feature.the MCV is usually > 100 fL. Some of the neutrophils are hypersegmented. There may be leucopenia due to reduction in granulocytes and lymphocytes and the platelet count may be moderately reduced. The severity of all these changes parallels the degree of anemia.(9)

Bone marrow - The marrow is hypercellular in the severely anemic patient. The cells are larger than normoblasts, and an increased number of cells with eccentric lobulated nuclei or nuclear fragments may be present. Giant and abnormally shaped metamyelocytes and enlarged hyperpolypoid megakaryocytes are characteristic.

Wendy P J den Elzen et al in 2010 did a systematic review about the association between subnormal vitamin B_{12} concentrations and anemia in older people(10).

Van Asselt et al in **2000** did a study about the clinical significance of low cobalamin levels in older hospital patients(11). In this prospective observational cohort design, study involved 28 patients aged 65 years and older with low plasma Cbl (150 pmol/ l). A number of haematological , metabolic and gastrointestinal parameters, and the response to Cbl treatment, were measured. Cbl deficiency was considered to be present when at least one of the following three criteria was fulfilled: (1) haematological or metabolic abnormalities compatible with Cbl deficiency; (2) Cbl malabsorption or atrophic gastritis; (3) a response to Cbl supplementation.

Vitamin B_{12} deficiency and Neuropathy

The existence of vitamin B_{12} deficiency neuropathy was recognized in 1958. The neurologic manifestation of cobalamin deficiency is less well understood but CNS demyelination may occur which may be due to reduced S-adenosyl methionine (SAM) or elevated methylmalonic acid (MMA). Another cause may involve adenosylcobalamin, a mitochondrial cofactor in the conversion of L-methylmalonyl CoA to succinyl CoA. Vitamin B_{12} deficiency leads to an increase in L-methylmalonyl CoA which is converted to D-methylmalonyl CoA and hydrolyzed to MMA.

Elevated MMA results in abnormal myelination leading to defective nerve transmission.

SUBACUTE COMBINED DEGENERATION OF THE CORD(12)

It is also termed as Posterolateral sclerosis or Combined system disease.

DEFINITION

It is a deficiency disease, usually associated with pernicious anemia, and characterized pathologically by degeneration of the white matter of the spinal cord,which is most evident in the posterior and lateral columns, and of the peripheral nerves and brain, and clinically by paraesthesiae, impairment of position and joint sense, sensory ataxia, and paraparesis. This was reviewed by **Healton EB** and **Lindenbaum J et al** in 1991 and later studied by **Savage DG** and **Lindenbaum J** in 1995(13,14). The clinical picture is usually due to combined features of posterior-column, corticospinal-tract, and peripheral-nerve degeneration, but involvement of the optic nerves and brain is not uncommon.

The onset of symptoms is usually gradual, but is sometimes rapid. The first symptoms are generally paraesthesiae, with tingling sensations, first felt in the tips of the toes, and later in the fingers. Other paraesthesias

often described include sensations of numbness, coldness, and tightness, while sharp stabbing pains ocassionally occur. Objective sensory changes are almost present, involving first the forms of sensibility mediated by the posterior columns. Postural sensibility and appreciation of passive movement and of vibration are impaired first in the lower, and later in the upper limbs. Cutaneous sensibility to light touch, pin-pick, heat, and cold is impaired at first in the periphery, leading to the characteristic ‘glove and stocking‘ distribution of superficial sensory loss. The calves may be tender on pressure. The proximal border of the anaesthetic areas may then ascend gradually.

In some cases weakness and spasticity predominate in the lower limbs while in others there may be predominance of sensory ataxia, but both weakness and sensory ataxia are usually present in the lower limbs, and are most severe in the lower with a positive Rhomberg’s sign. Moderate muscular wasting may develop in the later stages due to the peripheral neuropathy, and it mainly involves the peripheral muscles.

The reflexes vary considerably. In about 50 per cent of cases the ankle-jerks are absent when the patient is first seen; the knee-jerks are lost rather less frequently; in other cases both are exaggerated. The plantar reflexes are flexor at first in about half the cases, but later become

extensor in all but a few. When the degeneration is confined to the posterior columns, ataxia is the predominant symptom throughout and signs of corticospinal defect are lacking. Conversely, spastic paraplegia may alone be present while in yet other cases signs of peripheral neuropathy predominate.

Sphincter disturbances may occur in the form of urinary retention or incotinence. Impotence sometimes occurs early.

Bilateral primary optic trophy with some visual impairment is observed in about 5 per cent of cases and may even be the presenting feature with central scotoma (**Freeman and Heaton 1961**); Nystagmus is common. The pupils may be small, but react normally. Otherwise the cranial nerves are usually normal, though dysarthria occurs rarely.

Vitamin B_{12} Deficiency and Cognitive Impairment

There are many possible mechanisms through which low-normal vitamin B_{12} status could influence the functioning of the brain, and hence cognition, and these mechanisms are not mutually exclusive. One possibility is that the effect is mediated by homocysteine, because low vitamin B_{12} status is associated with an elevation of the concentration of tHcy. Many mechanisms have been proposed for the effects of

homocysteine on the brain, apart from an effect on the cerebral vasculature. Alternatively, the effect of low vitamin B_{12} status might be mediated by the raised concentrations of MMA, as discussed by McCracken et al; notably, the concentration of MMA in cerebrospinal fluid is twice that in plasma. Classical deficiency of vitamin B_{12} is accompanied by alterations in the concentrations of cytokines, such as tumor necrosis factor-α or epidermal growth factor. The commonest hypothesis, however, for the neurotoxic effects of low vitamin B_{12} status is that it leads to a deficiency of S-adenosylmethionine (SAM) and thereby to deficient methylation reactions in the central nervous system .

On a more global level, low-normal vitamin B_{12} status might mediate the effect on cognition by two mechanisms, atrophy of the brain and damage to the white matter. Progressive loss of brain tissue (atrophy) is well established as a factor associated with cognitive decline and dementia and recently it was shown that low-normal vitamin B_{12} status at baseline is a predictor of whole-brain atrophy in community-dwelling elderly. Progressive atrophy of the brain was associated with plasma vitamin B_{12} concentrations ranging from 800 to 160 pmol/L and with holotranscobalamin concentrations from 250 to 25 pmol/L. There was no obvious threshold concentration below which atrophy began.

Classical vitamin B_{12} deficiency is associated with damage to the white matter in the spinal cord and in the brain, which has been attributed to damage to myelin as a result of deficient methylation of myelin basic protein. There is much evidence that damage to the white matter in the brain is associated with, and may precede, cognitive decline. It is therefore noteworthy that, in participants in the Rotterdam scan study, damage to the white matter was related to vitamin B_{12} status over the normal range, as assessed by plasma total vitamin B_{12}, holotranscobalamin, transcobalamin saturation, and MMA. Previous case reports of patients with vitamin B_{12} deficiency reported that changes in the white matter are reversible with treatment with vitamin B_{12}.

Thus, it can be concluded that the cognitive deficit associated with low-normal vitamin B_{12} status may be due in part to loss of brain tissue over many years but also to potentially reversible damage to the white matter. However, to find out whether these associations are causal requires intervention studies.

Addison in 1849 noticed that “The mind occasionally wanders” in his patients which was cited by **McCaddon(15).**

Barrett in 1913 described histopathological changes in the cerebral cortex, notably neurodegeneration and damage to the white matter and blood vessels(16).

The idea that low-normal concentrations of vitamin B_{12} might be associated with cognitive impairment was raised by **Bell et al** in 1990 (17) and clearly expressed by **Rosenberg and Miller** in their seminal review 2 years later(18).

Bernard MA et al in 1998 examined the effect of vitamin B_{12} deficiency on older veterans and its relationship to general health and cognitive impairment(19).

Prevalence of vitamin B_{12} deficiency among demented patients and cognitive recovery with cobalamin replacement was studied by **Abyad A** in 2002(20) and by **Andres E** and **Kaltenbach G** in 2003(21).

Joshua W Miller in 2006 assessed the association between vitamin B12 status and cognitive function in older adults, but the findings were inconsistent(22).

A. David Smith and Helga Refsum in 2009 reviewed that cognition in the elderly may also be affected at concentrations of vitamin B12 above the traditional cutoffs for deficiency(23).

Laboratory diagnosis

Serum cobalamin should be measured whenever there is suspicion of vitamin B_{12} deficiency. The method now used is a commercial radioisotope dilution assay (or chemiluminescence assay). The normal range used in our study is 211-946 pg/mL.With this method a serum B12 level of less than 100 pg/mL is associated with neurological symptoms and signs of vitamin B_{12} deficiency. A level below 200 pg/mL that is not associated with symptoms requires further investigation of cobalamin deficiency. High serum concrntrations of cobalamin metabolites-methylmalonic acid (normal range, 73 to 271 nmol/L) and homocysteine (normal range 5.4 to 16.2 mmol/L) are probably the most reliable indicators of an intracellular cobalamin deficiency and can be used to corroborate the diagnosis.

About 90% of older patients with serum cobalamin levels less than 200 pg/mL show evidence of true tissue cobalamin deficiency, but individuals with neuropsychiatric disorders attributed to cobalamin deficiency may not have anemia and may have normal or minimally depressed cobalamin levels. Indeed, mild and usually subclinical cobalamin deficiency has been recognized in up to a quarter of free-living elderly (75 to 80 years of age). A falsely raised cobalamin level in the

presence of a true cobalamin deficiency will lead to clinical manifestations if uncorrected. Examples include an artificial increase in transcobalamin I and II, which can occur with myeloproliferative states, hepatomas, and fibrolamellar hepatic tumors; when transcobalamin II–producing macrophages are activated in autoimmune diseases, monoblastic leukemias, and lymphomas; and on release of cobalamin from hepatocytes during active liver disease in cobalamin-deficient patients. Studies suggest that approximately 10% of the U.S. population, especially the elderly, have true cobalamin deficiency manifested by low or low-normal serum cobalamin levels, as well as elevated levels of serum methylmalonic acid (MMA) and homocysteine that fall to normal with cobalamin therapy

Matchar et al did a study in **1994** to determine the use in routine clinical practice of the cobalamin serum assay in evaluating patients suspected of having cobalamin deficiency(24). The design was a prospective observational study of a diagnostic test compared with a criterion gold standard.

Pennypacker LC, Allen RH, Kelly JP et al in 1992 measured the prevalence of cobalamin (vitamin B_{12}) deficiency in geriatric outpatients as documented by both low serum cobalamin levels and elevations of

serum methylmalonic acid and homocysteine and to determine the response to cobalamin treatment(25). The prevalence was found to be very high (14.5%).

Clarke R and Refsum et al did a screening for vitamin B12 deficiency in older persons by measurement of serum homocysteine and methylmalonic acid (MMA) which were useful in borderline vitamin B12 deficiency(26).

Treatment

The traditional treatment for B_{12} deficiency has been intramuscular injections. However, since as early as 1968, oral vitamin B_{12} has been shown to have an efficacy equal to that of injections in the treatment of pernicious anemia and other B_{12} deficiency states.

Intramuscular injections, although safe and inexpensive, have several drawbacks. Injections are painful, medical personnel giving the injections are placed at risk of needlestick injuries, and administration of intramuscular injections often adds to the cost of therapy. Treatment schedules for intramuscular administration vary widely but usually consist of initial loading doses followed by monthly maintenance injections. One regimen consists of daily injections of 1,000 mcg for one

to two weeks, then a maintenance dose of 1,000 mcg every one to three months.

Although the daily requirement of vitamin B_{12} is approximately 2 mcg, the initial oral replacement dosage consists of a single daily dose of 1,000 to 2,000 mcg. This high dose is required because of the variable absorption of oral vitamin B_{12} in doses of 500 mcg or less. This regimen has been shown to be safe, cost-effective, and well tolerated by patients.

Schedule for Vitamin B_{12} Therapy

Oral route –initial dose of 1,000 to 2,000 mcg per day for one to two weeks followed by maintenance dose of 1,000 mcg per day for life.

Intramuscular route – initial dose of 100 to 1,000 mcg every day or every other day for one to two weeks followed by 100 to 1,000 mcg every one to three months.

Follow-Up

After the diagnosis of vitamin B_{12} deficiency has been made and a treatment plan has been initiated, follow-up is important to determine the patient's response to therapy. If vitamin B_{12} deficiency is associated with severe anemia, correction of the deficiency state should lead to a marked

reticulocytosis in one to two weeks. In mild vitamin B_{12} deficiency, repeat measurements of serum vitamin B_{12}, homocysteine, and methylmalonic acid levels should be done two to three months after initiating treatment.

AIM AND OBJECTIVES

1. To identify the prevalence of vitamin B_{12} deficiency in 100 consecutive patients aged 65 and above attending the geriatric o.p at Rajiv Gandhi Government General hospital.

2. To identify the prevalence of anemia, peripheral neuropathy and cognitive impairment in elderly due to Vitamin B_{12} Deficiency.

MATERIALS AND METHODS

STUDY CENTRE

Rajiv Gandhi Government General, Hospital, Chennai – 3.

TYPE OF STUDY

Cross sectional study

INCLUSION CRITERIA

1. Patients above 65 years attending geriatric outpatient department
2. Patients willing to participate in the study

EXCLUSION CRITERIA

1. Patients less than 65 years
2. Patients with Diabetes Mellitus
3. Patients with H/O chronic alcoholism
4. Patients with hypothyroidism

SAMPLE SIZE

100

METHODOLOGY

- Serum cobalamin in our study was measured using Chemiluminescence Immunosorbent Assay (C.L.I.A) which is a commercial radioisotope dilution assay.
- Hematologic evaluation was done by measuring hemoglobin and peripheral blood smear examination.
- Neurological assessment was done by examination of deep tendon reflexes and sensory system.
- Cognitive assessment was done using MMSE.

DATA COLLECTION & METHODS

Collection of data as per proforma with consent from patients in geriatric outpatient department.

ANALYSIS PLAN

1. Analyzing the prevalence of anemia, peripheral neuropathy and cognitive impairment
2. Analyzing the possible predisposing factors.
3. Data analyzed using statistical package – SPSS software

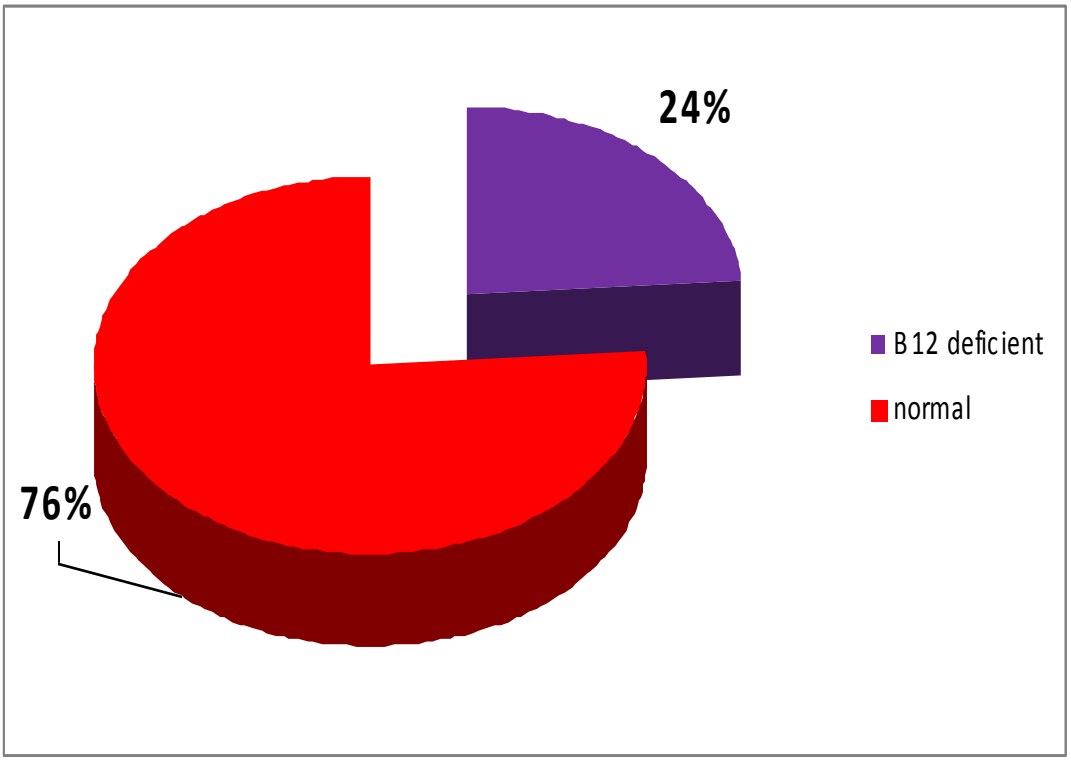
ETHICAL CLEARANCE

Obtained

RESULT & ANALYSIS

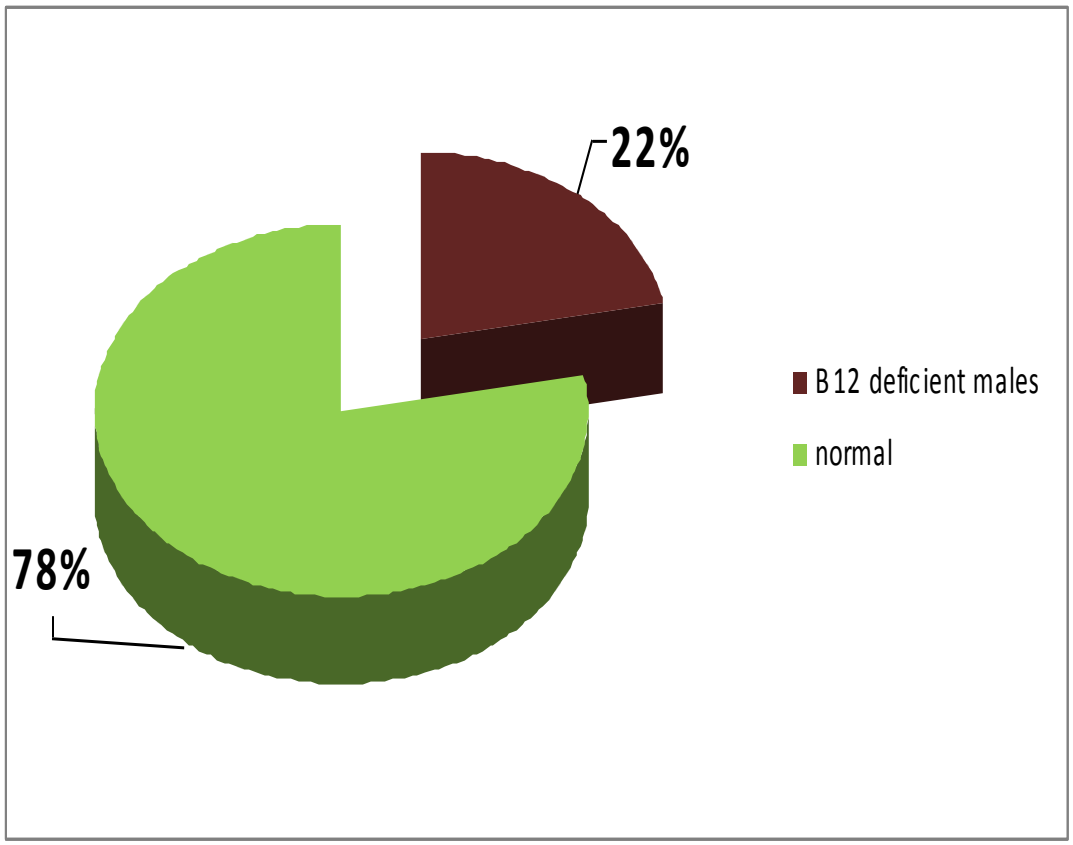
PREVALENCE OF VITAMIN B12

DEFICIENCY



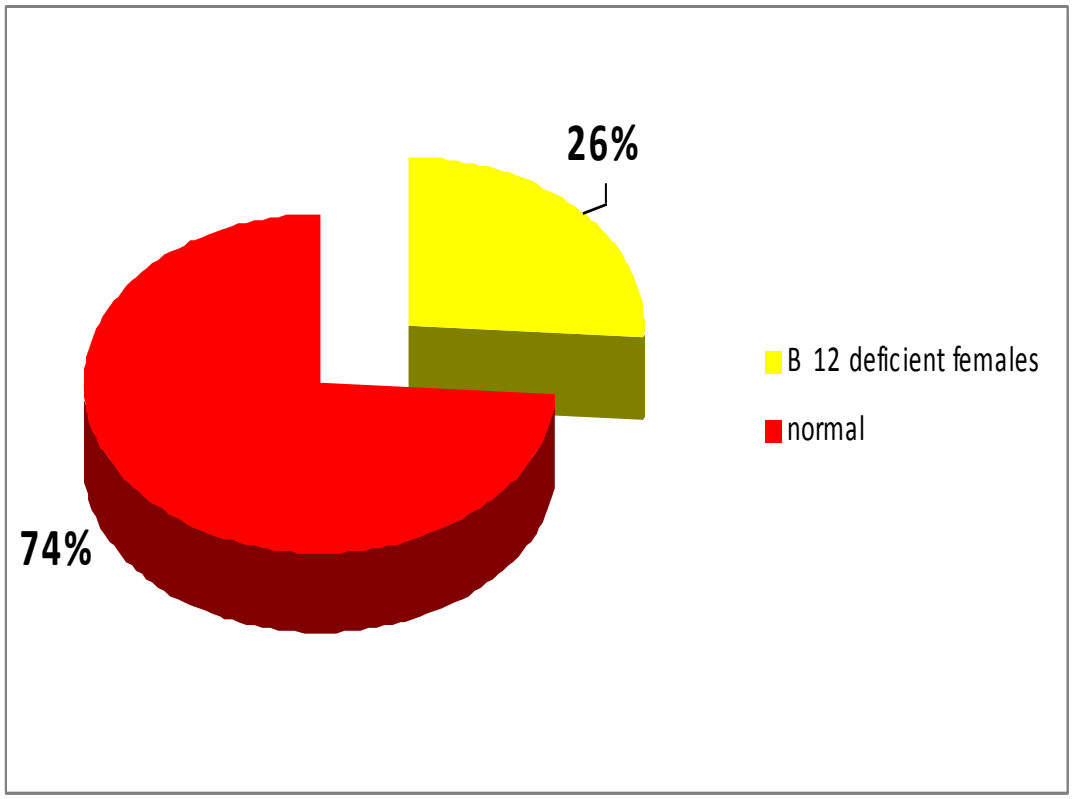
100 patients (50 males and 50 females) were included in the study, out of which 24 of them were found to be vitamin B_{12} deficient.

PREVALENCE IN MALES



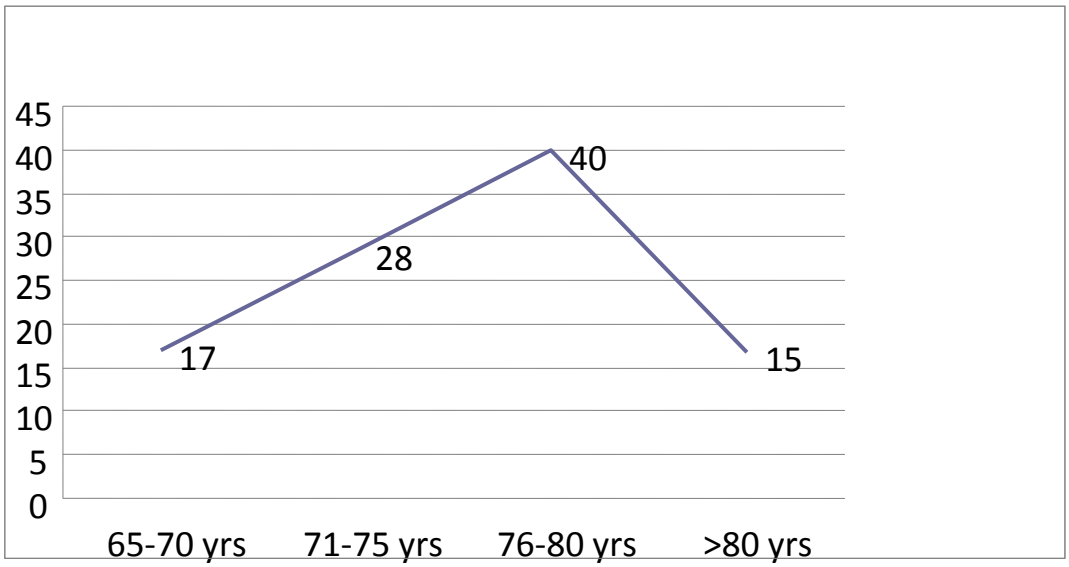
50 male patients were included in the study, out of which 11 had vitamin B_{12} deficiency with a prevalence of 22%.

PREVALENCE IN FEMALES



50 female patients were included in the study, out of which 13 had vitamin B12 deficiency with a prevalence of 26%.

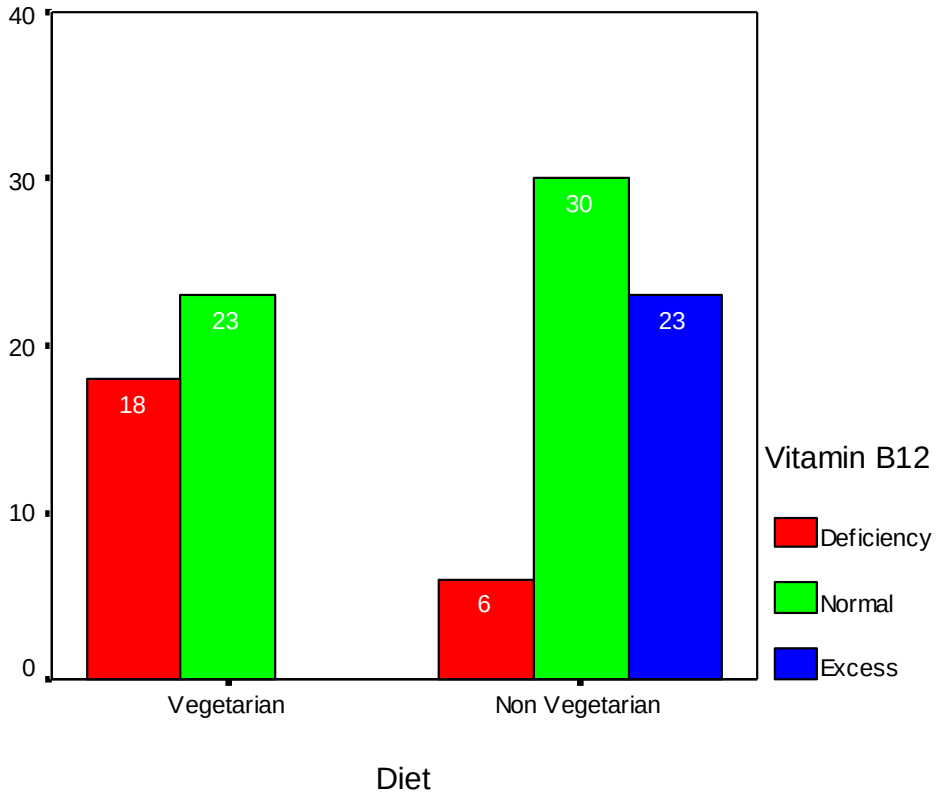
AGE DISTRIBUTION



Age group (in years)	Total number of patients	B12 deficient patients	Prevalence (%)
65-70	47	8	17
71-75	21	6	28
76-80	20	8	40
>80	12	2	15

DIET AND VITAMIN B12

DEFICIENCY



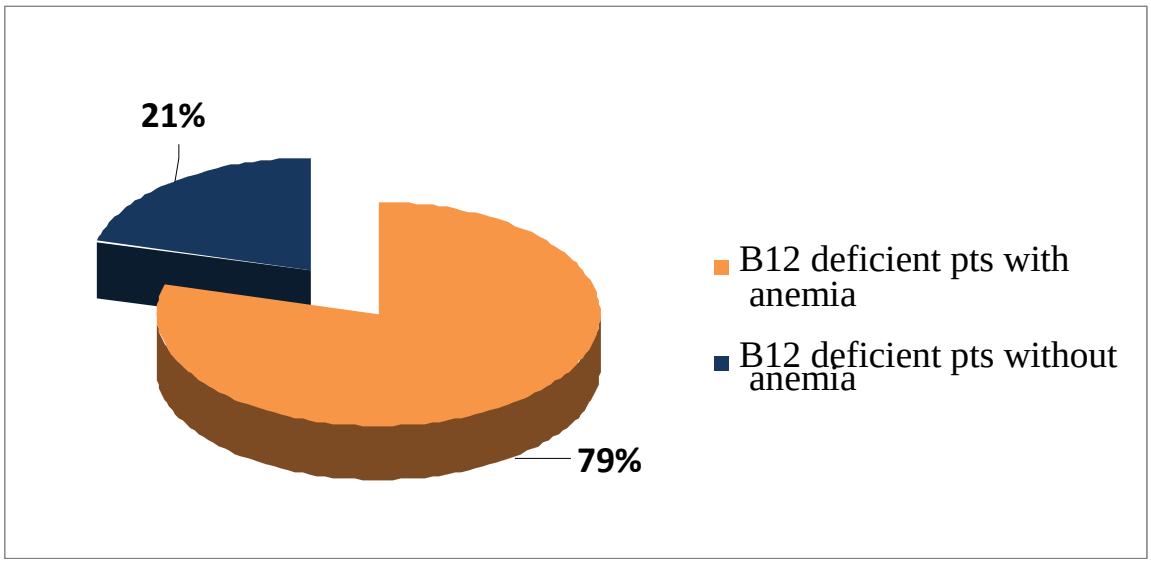
Vitamin B_{12} deficiency	**Vegetarians**	**Non-vegetarians**
Yes	18 (44%)	6 (10%)
No	23	53

In our study, 41 patients were vegetarians and 59 patients were non-vegetarians. Out of 41 vegetarians, 18 had vitamin B_{12} deficiency while 23 had normal levels indicating that the prevalence of vitamin B12 deficiency in vegetarians was 44%.

Out of 59 non-vegetarians 6 had low vitamin B_{12} levels, while 30 had normal levels and 23 of them had excess vitamin B_{12} levels.

P value is less than 0.0001 and the association was extremely statistically significant.

ANEMIA AND B12 DEFICIENCY

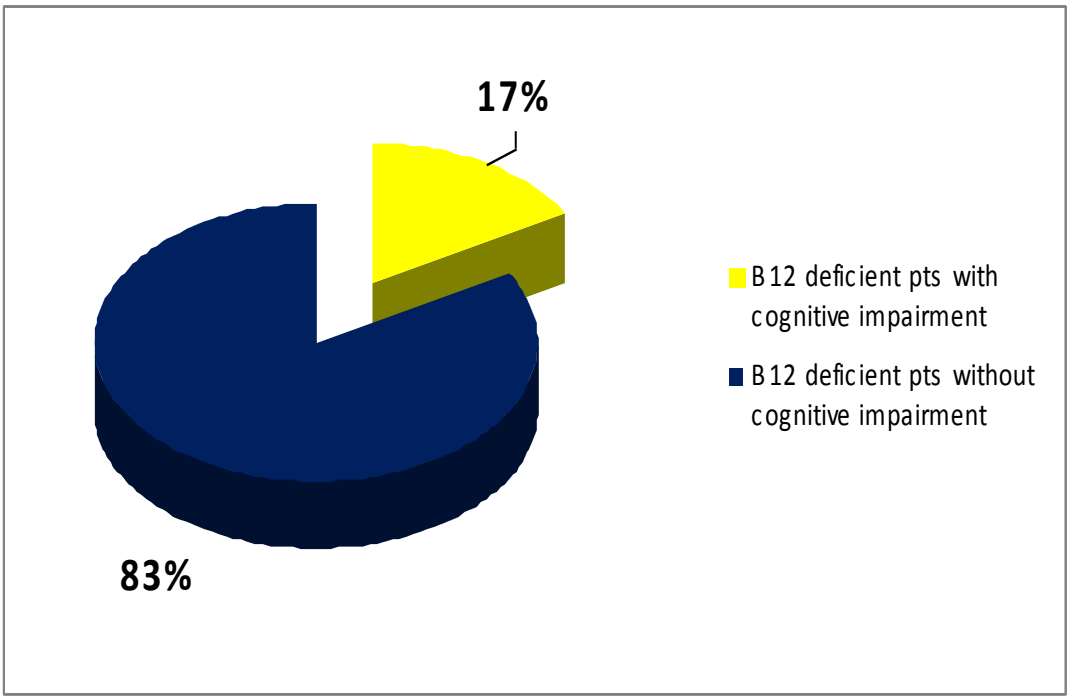


Number of patients with B_{12} deficiency = 24

Number of patients with anemia = 19 (Prevalence – 79%)

B12 DEFICIENCY AND COGNITIVE

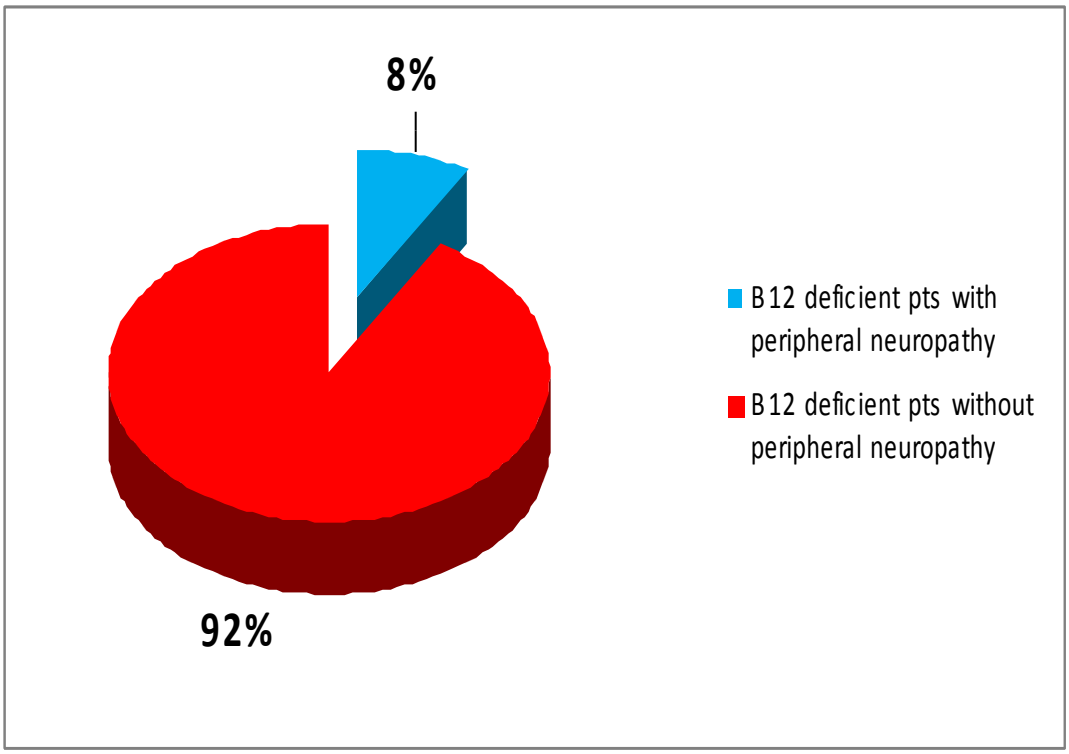
IMPAIRMENT



Number of patients with B_{12} deficiency = 24

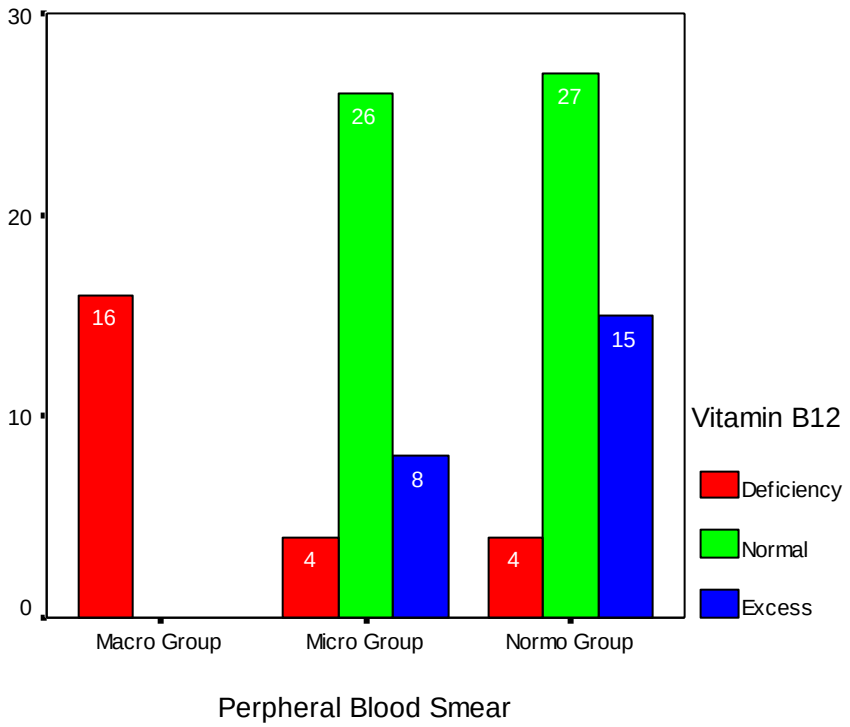
Number of patients with cognitive impairment = 4 (Prevalence – 16%)

B12 DEFICIENCY AND PERIPHERAL NEUROPATHY



Number of patients with B_{12} deficiency = 24

Number of patients with peripheral neuropathy = 2 (Prevalence – 8%)



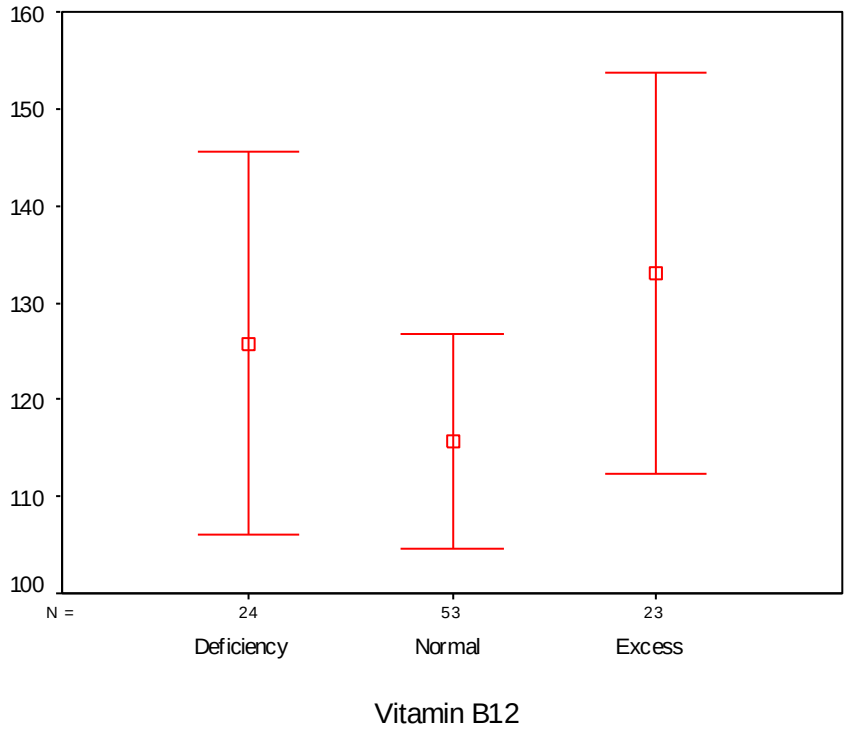
Number of patients with vitamin B_{12} deficiency = 24

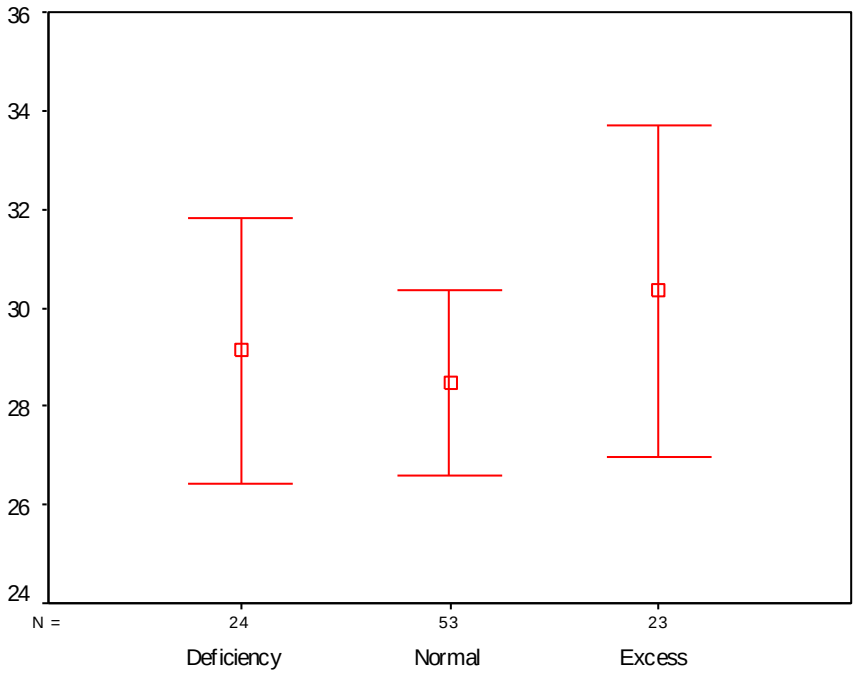
Number of patients with macrocytosis = 16 (prevalence 66%)

Number of patients with microcytosis = 4 (prevalence 16%)

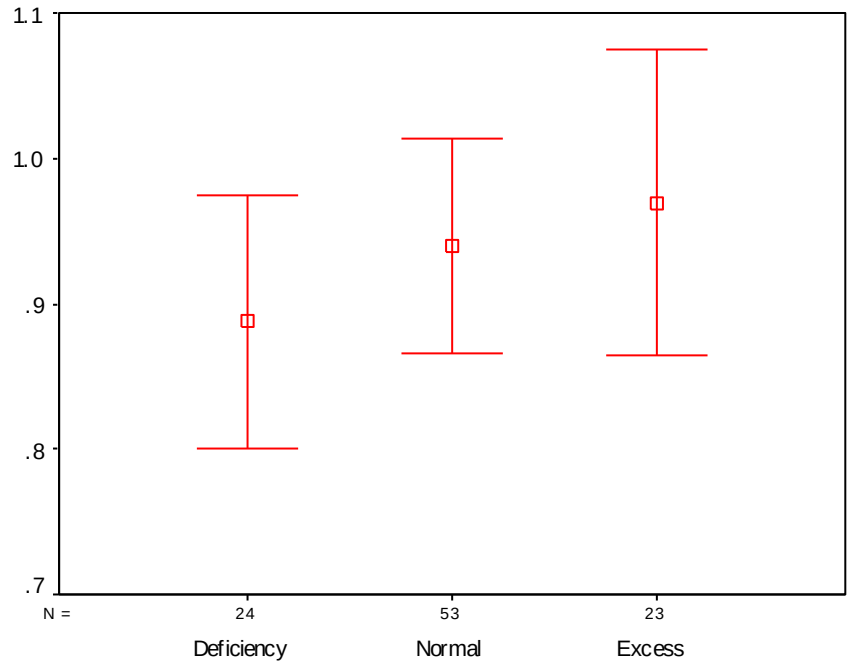
Number of patients with normocytosis = 4 (prevalence 16%)

The following diagram gives 95% confidence interval for blood sugar among people with vitamin B_{12} deficiency, normal and people with excessive vitamin B_{12}. If 100 such samples are taken then 95% samples will have mean values as indicated by a box in the middle of vertical line and will have a minimum and maximum as indicated by 2 horizontal lines connecting the vertical line.

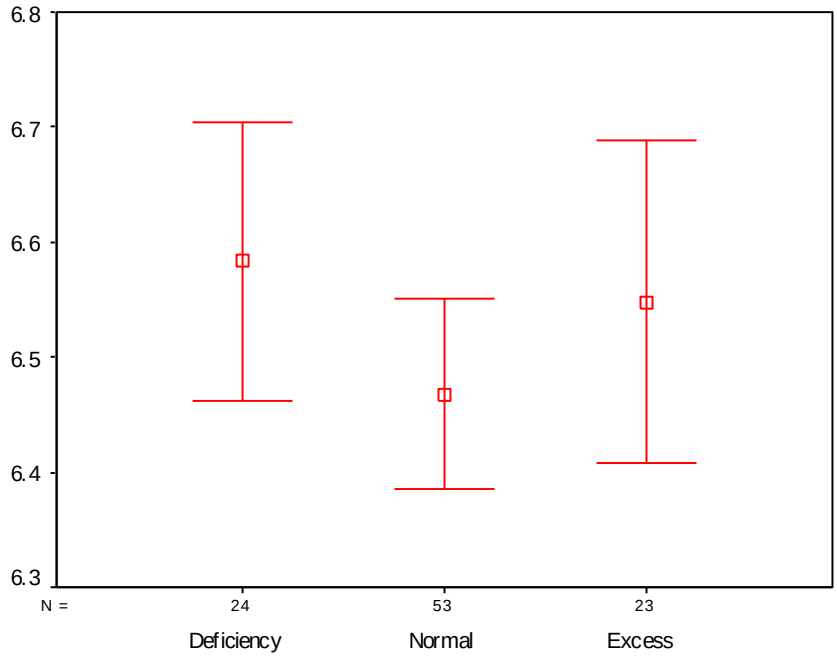




Vitamin B12



Vitamin B12



Vitamin B12

DISCUSSION

In our study 100 patients (50 males and 50 females) were included out of which 24 of them were found to be B_{12} deficient

Lindenbaum J and Rosenberg IH et al in 1994 determined the prevalence of cobalamin deficiency in Framingham elderly population. Out of 548 members in the study, serum cobalamin concentration < 258 pmol/L were found in 222 subject (40.5%)(27).

H.W. Baik and R.M. Russell in 1999 found that vitamin B_{12} deficiency is estimated to affect 10%-15% of people over the age of 60, and the laboratory diagnosis was based on low serum vitamin B_{12} levels or elevated serum methylmalonic acid and homocysteine levels(28).

Emmanuel Andres et al in 2004 found that vitamin B_{12} deficiency occurs frequently among elderly people and it was mainly due to food-cobalamin malabsorption syndrome (>60%), pernicious anemia (15%-20%), insufficient dietary intake and malabsorption(29).

Stabler and **Allen** in 2004 found that dietary vitamin B_{12} deficiency is a severe problem in the Indian subcontinent, Mexico, Central and South America, and selected areas in Africa but is not prevalent in Asia, except in vegetarians(30).

Also there are some studies done in India to determine the prevalence of vitamin B_{12} deficiency. Some of the data are as given below:

INDIAN SERIES	YEAR	VITAMIN B12 DEFICIENCY (%)
Mittal et al	1969	22.4
Gomber et al	1998	50.0
Chaudhry MW	2001	19.0
Chandra et al	2002	32.0
Khanduri et al	2005	33.0

The above data indicate that most of the values are in the same range as obtained in our study (24%)

SEX - WISE PREVALENCE

11 out of 50 males had vitamin B_{12} deficiency with a prevalence of 22% while 13 out of 50 females had vitamin B_{12} deficiency with a prevalence of 26% indicating females had more chances of developing B_{12} deficiency

AGE – GROUP WISE PREVALENCE

In the study 47 patients were in the age group of 65-70 years, out of which 8 had vitamin B_{12} deficiency with a prevalence of 17%

21 patients were in the age group of 71-75 years, out of which 6 had vitamin B12 deficiency with a prevalence of 28%

20 patients were in the age group of 76-80 years, out of which 8 had vitamin B12 deficiency with a prevalence of 40%

12 patients were in the age group above 80 years, out of which 2 had vitamin B12 deficiency with a prevalence of 16%

The above data indicates that prevalence of vitamin B_{12} deficiency increased steadily till the age of 80, after which it shows a gradual decline.

DIET AND VITAMIN B12 DEFICIENCY

In our study, 41 patients were vegetarians and 59 patients were non-vegetarians. Out of 41 vegetarians, 18 had vitamin B_{12} deficiency while 23 had normal levels indicating that the prevalence of vitamin B_{12} deficiency in vegetarians was 44%.

Out of 59 non-vegetarians 6 had low vitamin B_{12} levels, while 30 had normal levels and 23 of them had excess vitamin B_{12} levels.

Using the Pearson Chi-Square test, the association between vegetarian diet and vitamin B_{12} deficiency was found to be extremely stastically significant. (p value < 0.0001).

RELATIONSHIP BETWEEN VITAMIN B_{12} DEFICIENCY AND BLOOD SUGAR, BLOOD UREA, SERUM CREATININE AND SERUM PROTEIN

If mean values of more than two groups are to be compared, then One way Analysis Of Variance (ANOVA) has to be applied. In the present study, it is of interest to know whether vitamin B_{12} deficiency has got any effect on blood sugar. blood urea, serum creatinine and serum protein of patients. These levels are compared with 3 groups of people namely, vitamin B_{12} deficient people, normal people and people having excess of vitamin B_{12}.

Null hypothesis that is being tested is that mean levels of three groups compared with reference to each one of the four levels are the same. Null hypothesis has to be rejected if significance value of ANOVA is less than 0.05. Otherwise there is no reason to reject the null

hypothesis. In the present study significant value of all the four levels are greater than 0.05 and hence we conclude that neither blood sugar, blood urea, serum creatinine or serum protein has any effect over vitamin B_{12} deficiency.

Student t test is used to compare the mean values of two groups at a time. The null hypothesis assumed in t test is that mean value of two groups compared are the same against the alternative that mean values are not the same.

VITAMIN B_{12} DEFICIENCY AND ANEMIA

Out of the 24 patients with vitamin B12 deficiency, 19 had anemia with a prevalence of 79%. Also 32 out of 53 people with normal B_{12} levels had anemia with a prevalence of 60% while 11 out of 23 people with vitamin B12 excess had anemia with a prevalence of 47%.

VITAMIN B_{12} DEFICIENCY AND PERIPHERAL BLOOD SMEAR

Out of the 24 patients with vitamin B_{12} deficiency, 16 presented with macrocytosis with a prevalence of 66% while 4 persons presented with microcytosis with a prevalence of 16% whereas remaining 4 persons were normocytic.

VITAMIN B_{12} DEFICIENCY AND PERIPHERAL NEUROPATHY

Out of 24 patients with vitamin B_{12} deficiency, 7 had complaints of numbness and paraesthesis, while 17 did not. 11 out of 53 patients with normal B_{12} levels had similar complaints while out of 23 patients with excess B_{12} levels 8 had the complaints.

Out of 24 patients with vitamin B_{12} deficiency, 2 had peripheral neuropathy with a prevalence of 8%. Also 4 out of 53 people with normal B_{12} levels had peripheral neuropathy with a prevalence of 7% while it was found in 5 out of 23 people with excess B_{12} levels with a prevalence of 21%.

VITAMIN B_{12} DEFICIENCY AND COGNITIVE IMPAIRMENT

Out of 24 patients with vitamin B_{12} deficiency, 4 had cognitive impairment with a prevalence of 16%. Also 7 out of 53 people with normal B_{12} levels had cognitive impairment with a prevalence of 13% whole was found in 5 out of 23 people with excess B_{12} levels with a prevalence of 21%.

In clinical practice, it is found that patients with cognitive impairment associated with vitamin B_{12} deficiency often improve on treatment, whereas those with obvious dementia usually show no

improvement. However, these are essentially anecdotal reports and there have been very few randomized controlled trials in which vitamin B_{12} alone has been given to elderly people with cognitive impairment or dementia. The Cochrane review in 2003 could find only 2 trials with acceptable methodology, which had a total of 42 patients enrolled, of whom only 36 completed the trials. Treatment periods were 1 or 5 mo. The endpoints were changes in the Mini-Mental State Examination or Alzheimer's Disease Assessment Scale–Cognitive, which assess global cognitive abilities: no difference was found between treated and placebo groups. A recent systematic review identified 6 trials that satisfied their methodologic criteria, but the wide variety of doses used and the 35 different cognitive function tests made it difficult to come to any conclusion. Notably, some of the trials reported a worsening of cognition in the vitamin B_{12} treated groups compared with those receiving placebo. But in 4 of the 6 trials, the participants were normal elderly without cognitive impairment. It is clear that no conclusions can be drawn from the published trials. The trials have all been underpowered, too short in duration, and often carried out on the wrong type of subject. It can be concluded that “Large randomized trials are required to evaluate the value of vitamin B_{12} for improving cognitive function and preventing or retarding cognitive decline in normal and demented older people. Trials

need to use established and validated diagnostic criteria and measures of cognitive function and to be long enough to detect trends".

Given the complexity of the mechanisms related to cognitive changes in the elderly, and the metabolic relationship between B vitamins and homocysteine levels, the association between B-vitamin status and subsequent cognitive function remains unclear. This systematic review of observational studies investigates the association between blood levels or dietary intake of B vitamins and the risk and progression of neurocognitive deficit as measured by cognitive tests and age-related neurodegenerative disorders such as Alzheimer's disease in humans.

CONCLUSION

1. Out of the 100 consecutive patients studied 24 of them were found to be Vitamin B_{12} deficient.

2. A strong association between B_{12} deficiency and anemia was noted but not with peripheral neuropathy and cognitive impairment.

3. Association between vegetarian diet and B_{12} deficiency was found to be extremely statistically significant. (P value < 0.0001)

4. Prevalence of Vitamin B_{12} deficiency increased steadily till the age of 80 after which it showed a gradual decline.

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ABBREVIATIONS

MMSE	–	Mini-Mental Status Examination
MMA	-	MethylMalonic Acid
Cbl	-	Cobalamin
H2 blockers	–	Histamine-2 blockers
PPIs	–	Proton pump inhibitors
IF	-	Intrinsic Factor
TC I	-	Transcobalamin I
TC II	–	Transcobalamin II
HCs	-	Haptocorins
SAM	-	S – adenosyl methionine
THF	-	Tetra Hydro Folate

PROFORMA

NAME:

AGE:

SEX:

OP NO:

ADDRESS:

PAST HISTORY:

1. Diabetes Mellitus
2. Hypothyroidism
3. Alcoholism
4. Drug intake

H/O EASY FATIGUABILITY:

H/O NUMBNESS AND PARATHESIA:

H/O MEMORY DISTURBANCES:

MMSE SCORE : / 30

SENSORY SYSTEM EXAMINATION

TOUCH

TEMPERATURE

PAIN

VIBRATION

JOINT POSITION

INVESTIGATIONS

1. HEMOGLOBIN
2. RENAL FUNCTION TEST
   - Sugar
   - Urea
   - Creatinine
3. PERIPHERAL BLOOD SMEAR
4. THYROID FUNCTION TEST
5. VITAMIN B_{12} LEVEL

TICK WHICHEVER IS APPLICABLE

ANEMIA ☐

PERIPHERAL NEUROPATHY ☐

DEMENTIA ☐

"Mini-Mental" status test of Folstein, Folstein, and McHugh

TASK	INSTRUCTIONS	SCORING	
Date orientation	"Tell me the date?" Ask for omitted items.	One point each for year, season, date, day of week, and month	5
Place orientation	"Where are you?" Ask for omitted items.	One point each for state, county, town, building, and floor or room	5
Register three	Name three objects slowly and objects clearly. Ask the patient to repeat them.	One point for each item correctly repeated	3
Serial sevens	Ask the patient to count backwards from 100 by 7. Stop after five answers. (Or ask them to spell "world" backwards.)	One point for each correct answer (or letter)	5
Recall three objects	Ask the patient to recall the objects mentioned above.	One point for each item correctly remembered	3
Naming	Point to your watch and ask the patient "what is this?" Repeat with a pencil.	One point for each correct answer	2
Repeating a phrase	Ask the patient to say "no ifs, ands, or buts."	One point if successful on first try	1
Verbal commands	Give the patient a plain piece of paper and say "Take this paper in your right hand, fold it in half, and put it on the floor."	One point for each correct action	3

Written commands	Show the patient a piece of paper with “CLOSE YOUR EYES” printed on it.	One point if the patient’s eyes close	1
Writing	Ask the patient to write a sentence.	One point if sentence has a subject, a verb, and makes sense	1
Drawing	Ask the patient to copy a pair of intersecting pentagons onto a piece of paper.	One point if the figure has ten corners and two intersecting lines	1
Scoring	**A score of 24 or above is considered normal.**		**30**

TITLE: PREVALENCE OF VITAMIN B12 DEFICIENCY IN ELDERLY

AUTHORS: Dr. Bijin Oliver John, Post Graduate Dr. G.Usha, M.D, Asst Prof, Dept of GeriatricsDr. S.Deepa, M.D, Asst Prof, Dept of GeriatricsDr. B.Krishnaswamy, M.D, Prof and HOD, Dept of Geriatric Medicine.

INTRODUCTION : Low serum B12 levels become more common with aging. it has been recently found that approximately 10% to 15% of older patients have vitamin B12 deficiency. **AIMS AND_OBJECTIVES_** : To identify prevalence of vitamin B12 deficiency in 100 patients aged 65 and above and to identify prevalence of anemia, peripheral neuropathy and cognitive impairment in elderly due to vitamin B12 deficiency **. STUDY DESIGN**: Cross-sectional study . SAMPLE SIZE: 100 .**METHODOLOGY**:INCLUSION CRITERIA:1. Patients above 65 years attending geriatric outpatient department 2. Patients willing to participate in the study. EXCLUSION CRITERIA:1. Patients less than 65 years 2. Patients with Diabetes Mellitus3. Patients with hypothyroidism4. H/o alcoholism/drug intake/GI surgery. 100 patients attending geriatric outpatient (50 males and 50 females) were screened for vitamin B 12 deficiency by assay and then evaluated for presence of anemia, peripheral neuropathy and cognitive impairment by clinical methods and laboratory investigations. **RESULTS** : Out of the 100 consecutive patients studied 24 of them were found to be Vitamin B12 deficient. A strong association between B12 deficiency and anemia was noted but not with peripheral neuropathy and cognitive impairment. Association between vegetarian diet and B12 deficiency was found to be extremely statistically significant. (P value < 0.0001). Prevalence of Vitamin B12 deficiency increased steadily till the age of 80 after which it showed a gradual decline.

KEY WORDS : vitamin B12, anemia, peripheral neuropathy, cognitive impairment, elderly,homocysteine.